

Coronary Artery Spasm as a Frequent Cause of Acute Coronary Syndrome

The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study

Peter Ong, MD, Anastasios Athanasiadis, MD, Stephan Hill, MD, Holger Vogelsberg, MD, Matthias Voehringer, MD, Udo Sechtem, MD

Stuttgart, Germany

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| Objectives | This study was conducted to clarify the incidence of coronary spasm in emergency patients with suspected acute coronary syndrome (ACS) and acute chest pain at rest. |
| Background | Chest pain at rest is a frequent symptom in the emergency room. Acute coronary syndrome is suspected in patients with elevation of cardiac markers, ischemic electrocardiographic changes, or simply typical clinical symptoms of unstable (usually resting) angina. However, of all patients with suspected ACS who undergo coronary angiography, up to 30% have nonobstructed coronary arteries. We sought to clarify how many of these patients suffer from coronary spasm as a possible cause of their chest pain. |
| Methods | In a prospective study from June to December 2006, all patients with suspected ACS who underwent coronary angiography and had no culprit lesion underwent intracoronary provocation with acetylcholine. The ACH testing was considered positive at a vasoconstriction of $\geq 75\%$ relative to the diameter after intracoronary nitroglycerine when the initially reported symptoms could be reproduced. |
| Results | Of 488 consecutive patients, 138 had no culprit lesion (28%). Twenty-two were found to have another diagnosis. The ACH testing was performed in 86 of the remaining 116 patients. In 42 patients, coronary spasm was verified (49%). |
| Conclusions | Every fourth patient with ACS had no culprit lesion. Coronary spasm could be documented in nearly 50% of the patients tested by ACH. Coronary spasm is a frequent cause of ACS and should regularly be considered as a differential diagnosis. (J Am Coll Cardiol 2008;52:523-7) © 2008 by the American College of Cardiology Foundation |

Chest pain at rest is one of the most frequent symptoms of patients in the emergency room (1). The diagnosis of acute coronary syndrome (ACS) is suspected in these patients, especially when typical electrocardiographic (ECG) changes and/or elevation of cardiac markers can be detected. However, of all patients who undergo coronary angiography because of suspected ACS, up to 30% have unobstructed coronary arteries or at least no culprit lesion that could explain the patient's discomfort (2,3). Potential other causes for the clinical symptoms encompass a variety of diagnoses.

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Possible extracardial causes can be pulmonary, gastroesophageal, musculoskeletal, or psychiatric (4). Apart from coro-

nary embolism or thrombosis (5), diseases such as myocarditis (6) or tako-tsubo-cardiomyopathy (7) have also been described in these patients.

Coronary spasm is another well-defined mechanism for ACS causing ischemia at rest (8). However, only 2 studies examined the frequency of coronary spasm in patients with ACS and unobstructed coronary arteries. Whereas a high prevalence (74%) of ergonovine-provoked coronary spasm was found in a Taiwanese population (8), a similar study in Caucasian patients documented coronary spasm only in 16% (9). Therefore, we sought to prospectively investigate the frequency of coronary spasm in patients with ACS including all presentations (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], unstable angina pectoris [UAP]) who showed no culprit lesion or hemodynamically relevant stenosis ($>50\%$) at coronary angiography. Intracoronary provocation for coronary spasm was done using acetylcholine (ACH) (10).

From the Department of Cardiology and Pulmology, Robert-Bosch-Krankenhaus, Stuttgart, Germany.

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Abbreviations
and Acronyms

ACH = acetylcholine
ACS = acute coronary syndrome
ECG = electrocardiogram
LCA = left coronary artery
NSTEMI = non-ST-segment elevation myocardial infarction
STEMI = ST-segment elevation myocardial infarction
UAP = unstable angina pectoris

Methods

Patient population and ACH test. In a prospective study from June to December 2006, 488 consecutive patients who underwent coronary angiography because of ACS were registered and written informed consent for an additional intracoronary ACH provocation was obtained. The study complied with the Declaration of Helsinki. We defined ACS as acute chest pain (i.e., chest pain at rest >20 min within the last 48 h) together with ECG changes suggesting

myocardial ischemia and/or elevation of cardiac markers (11). In case of detection of a culprit lesion, percutaneous coronary intervention was performed or coronary artery bypass grafting or conservative treatment was recommended. If coronary angiography revealed no culprit lesion, we conducted an ACH test. Incremental doses of 2, 20, and 100 μ g ACH were injected into the left coronary artery via the diagnostic catheter for 3 min each (10,12). If the test in the left coronary artery was negative, 80 μ g ACH was injected into the right coronary artery. When coronary spasm was demonstrated, 0.2 mg of Perlinganit (glyceroltrinitrate, Schwarz Pharma, Monheim, Germany) was injected into the responsible vessel.

The ACH test was performed either at primary catheterization or in a second session depending on the patient's condition and the administered medication. It was not performed in one of the following conditions: patient refusal, suspected myocarditis, tako-tsubo-cardiomyopathy, severe chronic obstructive pulmonary disease, severe renal insufficiency, allergy to iodinated contrast media.

Quantitative analysis. All ACH tests were quantitatively analyzed with QCA-CMS 7.0 (Medis-Software, Leiden, the Netherlands). The ACH test was positive when the visual findings at coronary angiography and the quantitative analysis confirmed a vasoconstriction of $\geq 75\%$ compared with the relaxed state after intracoronary administration of glyceroltrinitrate together with a reproduction of the patient's initial symptoms (10,13,14).

Statistics. Results are expressed as mean \pm standard deviation. The *t* test was used to compare continuous variables. For values without normal distribution, median and interquartile ranges are stated and Mann-Whitney *U* test was used. The chi-square test was used for categorical and ordinal variables. A two-tailed *p* value <0.05 was considered significant. Data analysis was done with SPSS 14.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics. A total of 488 patients were included (Table 1). They were divided into 2 groups depending on the presence or absence of a culprit lesion at coronary angiography. Patients with culprit lesion were older, were more often male, and showed significantly higher levels of cardiac markers. In addition, these patients had a significantly lower left ventricular ejection fraction. There was a higher prevalence of diabetes mellitus in the group with culprit lesion (*p* = 0.002). The distribution of ACS in the 2 groups is shown in Figure 1. In patients with culprit lesion, STEMI and NSTEMI were significantly more prevalent than in patients without culprit lesion (*p* < 0.001).

Patients without culprit lesion. We identified 138 patients without culprit lesion. In 22 patients, the diagnosis could be determined before the ACH test. Nine patients (6.5% of all patients without culprit lesion) had myocarditis that was diagnosed by cardiac magnetic resonance imaging

Table 1 Patient Main Clinical Characteristics

| | All Patients | Culprit Lesion Present | Culprit Lesion Absent | p Value |
|--------------------------------|-------------------|------------------------|-----------------------|---------|
| n | 488 | 350 | 138 | |
| Gender, male | 315 (64.5%) | 249 (71.1%) | 66 (47.8%) | <0.0001 |
| Age, yrs (mean \pm SD) | 66 (\pm 12) | 67 (\pm 12) | 62 (\pm 13) | <0.0001 |
| Risk factors | | | | |
| Hypertension | 310 (70.6%) | 223 (71.9%) | 87 (67.4%) | NS |
| Diabetes mellitus | 126 (28.8%) | 102 (33%) | 24 (18.6%) | 0.002 |
| Hypercholesterolemia | 262 (59.8%) | 189 (61.2%) | 73 (56.6%) | NS |
| Smokers | 118 (26.7%) | 90 (28.7%) | 28 (21.9%) | NS |
| Obesity | 69 (15.8%) | 48 (15.5%) | 21 (16.4%) | NS |
| Positive family history of CVD | 141 (32.3%) | 87 (28.1%) | 54 (42.2%) | 0.001 |
| Cardiac markers and LVEF | | | | |
| LVEF, % (IQR) | 61 (47–71) | 56 (44–69) | 59 (39–69) | <0.001 |
| TnI, μ g/l, n < 0.16 (IQR) | 1.70 (0.04–22.01) | 6.41 (0.49–51.76) | 0.02 (0.02–0.28) | <0.001 |
| CK, U/l, n < 180 (IQR) | 143 (69–599) | 332 (115–714) | 83 (56–128) | <0.001 |
| BNP, pg/ml, n < 80 (IQR) | 193 (67–600) | 247 (80–1018) | 59 (25–178) | <0.001 |

BNP = B-type natriuretic peptide; CK = creatine kinase; CVD = cardiovascular diseases; IQR = interquartile range; LVEF = left ventricular ejection fraction; NS = not significant; TnI = troponin I.

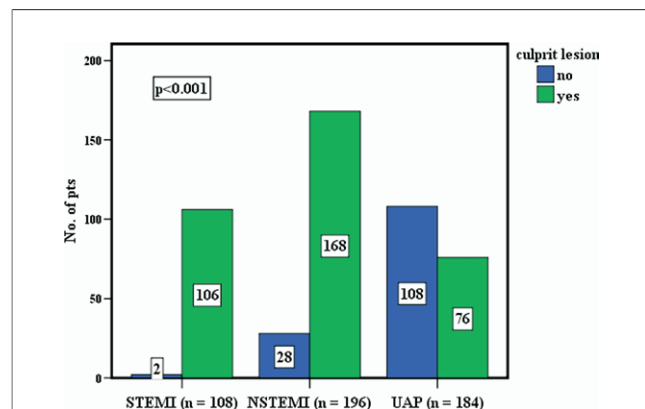


Figure 1 Presentation of ACS (n = 488)

Distribution of different presentations of ACS according to presence or absence of culprit lesion. ACS = acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

and later confirmed by endomyocardial biopsy, 7 patients had tako-tsubo-cardiomyopathy (5%), 1 patient had an acute bleeding, and 1 had pulmonary embolism. Four other patients already had a positive previous ACH test result and were hence assumed to have coronary spasm as the cause of their recurrent chest pain.

Eighty-six of the remaining 116 patients underwent the ACH test (74%). In 30 patients the ACH test could not be performed because of the abovementioned reasons. Coronary spasm was verified in 42 patients (49% of the patients who underwent the test and 30% of all patients without culprit lesion) (Table 2). The remaining 44 patients showed different patterns of reproduction of symptoms and vasoreaction (Fig. 2). Of all 86 patients without culprit lesion who underwent ACH testing, 7 patients showed significant troponin I

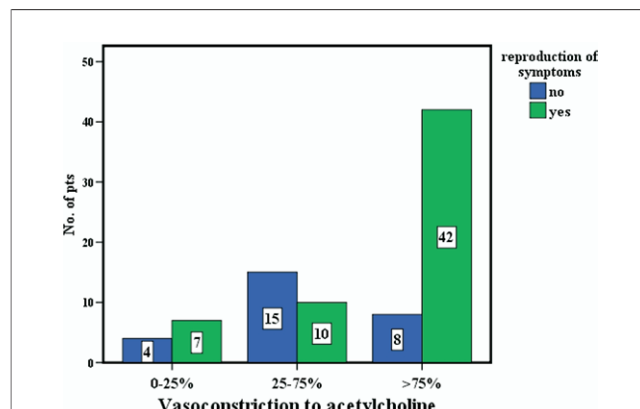


Figure 2 ACH Test (n = 86)

Distribution of different vasoreactions to acetylcholine (ACH) according to reproduction of the patient's initial symptoms.

elevation. Coronary spasm was found in 4 (57%) of them, which was not statistically different from the 43% (3 of 7) patients who had coronary spasm without marker elevation ($p = 0.696$). Thus, there was no association between troponin levels and spasm.

ACH test and ECG. Intracoronary admission of ACH reproduced exactly the same chest pain in 42 of 50 patients who had coronary spasm by angiography. The ECG of these 42 patients showed ischemic ST-segment changes during or after ACH administration (17 ST-segment depression, 3 ST-segment elevation) in 20 patients (48%). In 3 other patients who had only a 6-lead ECG, spasm was occlusive, which is highly likely to be associated with ischemia, but there were no visible changes in the 6-lead ECG. In 6 patients the ECG could not be interpreted (5 because of left bundle branch block, 1 because of pacemaker ECG). In the remaining 13 patients it was not possible to tell whether there were signs of ischemia in the ECG because of technical problems or only 6-lead registration.

Discussion

Almost 50% of our patients who underwent the ACH test had proof of coronary spasm. If one includes the 4 other patients who already had a positive previous ACH test result, this proportion increases to slightly above 50%. No other study in consecutive Caucasian patients has ever shown a plausible cardiac explanation for the occurrence of the clinical picture of ACS in such a high number of patients with normal coronary arteries.

All patients. Of patients with ACS included in our study, 72% had a culprit lesion at coronary angiography. Patients in this group were older and presented significantly more often with STEMI and NSTEMI than the group without a culprit lesion. Thus, it is not surprising that patients with a culprit lesion had a significantly lower left ventricular ejection fraction, higher levels of cardiac markers, and a

Table 2 Clinical Characteristics of Patients Without Culprit Lesion Who Had an Acetylcholine Test

| | Spasm Present | Spasm Absent | p Value |
|---|-------------------|------------------|---------|
| n | 42 | 44 | |
| Gender, male | 21 (50%) | 25 (56.8%) | NS |
| Age, yrs (median) | 60 (± 12) | 61 (± 11) | NS |
| Risk factors | | | |
| Hypertension | 27 (64.2%) | 29 (65.9%) | NS |
| Diabetes mellitus | 8 (19%) | 7 (15.9%) | NS |
| Hypercholesterolemia | 26 (61.9%) | 22 (50%) | NS |
| Smokers | 10 (23.8%) | 8 (18.1%) | NS |
| Obesity | 6 (14.2%) | 6 (13.6%) | NS |
| Positive family history of CVD | 22 (52.3%) | 21 (47.7%) | NS |
| Cardiac markers and LVEF | | | |
| LVEF, % (IQR) | 70 (62-79) | 71% (62-77) | NS |
| Tnl, $\mu\text{g/l}$, $n < 0.16$ (IQR) | 0.02 (0.02-0.03) | 0.02 (0.02-0.02) | NS |
| CK, U/l, $n < 180$ (IQR) | 73.5 (55.5-134.5) | 79 (49-120) | NS |
| BNP, pg/ml, $n < 80$ (IQR) | 48 (23-68) | 60 (22.5-176) | NS |

Abbreviations as in Table 1.

higher prevalence of diabetes mellitus. Patients with culprit lesions were more often male, confirming a previous observation of a higher prevalence of women in the group of patients with ACS but without significant coronary artery disease (15).

Patients without culprit lesion. In contrast to our results, Da Costa et al. (9) found that only 16% of French patients with myocardial infarction and normal coronary arteries had ergonovine-induced coronary spasm. A potential explanation for this discrepancy is the different inclusion criteria. Their patients had to have chest pain, ECG changes, and increased plasma enzyme activity, whereas our patients had to have chest pain at rest >20 min and only one of either ischemic ECG changes or elevation of cardiac markers. However, after matching our patients with the inclusion criteria of Da Costa et al. (9), we still found 50% of our patients with coronary spasm, which is 3 times more frequent than in their study.

Could the different method of application used to provoke coronary spasm explain the different proportions of vasospasm in the study by Da Costa et al. (9) and our study? Application of ergonovine in their patients was done intravenously, whereas we used intracoronary application of ACH. This methodical difference could have contributed to the lower percentage of positive tests in the study by Da Costa et al. (9). Goto et al. (16) showed that in patients with chest pain who underwent intravenous ergonovine testing with a negative result, additional intracoronary provocation with ACH could reveal coronary spasm in 79%.

In contrast to the Da Costa et al. (9) findings and more congruent with our observations, coronary spasm is an important differential diagnosis in Asian patients with ACS and unobstructed coronary arteries. Miwa et al. (17) studied the role of coronary spasm in Japanese patients with stable and unstable angina. Intracoronary infusion of ACH provoked coronary spasm in 93% of patients with unstable angina, which was significantly higher than in patients with stable angina (20%), who had organic stenoses $\geq 50\%$ ($p < 0.01$). However, 30% of their unstable patients also had fixed coronary stenoses ($\geq 50\%$) (17). Finally, Wang et al. (8) found in a Taiwanese population a high frequency of coronary spasm, especially in patients with troponin I-positive ACS and insignificant coronary artery disease. In 17 of 23 patients (74%), coronary spasm was provoked by intracoronary administration of ergonovine (8).

Although we found a higher incidence of coronary spasm in our population compared with a previous study in Caucasian patients, we could not reproduce the high proportion of patients with coronary spasm in the Asian populations with ACS. Because the higher prevalence of coronary vasospasm has also been documented in Asian populations with stable effort angina (18), this finding leads to the assumption that racial differences could explain the higher prevalence of spasm in the Asian populations. Clinically it has been observed that Japanese patients have a more diffuse coronary hyperreactivity with an increased

basal tonus. This might be a reason why coronary spasm can be observed in Japanese patients more often than in Caucasians, in whom coronary spasm is reported to be of a more localized nature (18).

One could therefore speculate that coronary spasm in our patients might be a response to some local arterial injury that could vanish after healing. Indeed, patients with coronary spasm had a significantly shorter time interval between onset of symptoms and ACH test than those without coronary spasm (mean: 47 h, interquartile range: 24 h to 48 h vs. mean: 65 h, interquartile range: 24 h to 96 h, Mann-Whitney *U* test). However, in the 16 patients in whom we performed ACH testing in all 3 coronaries, multivessel spasm was found in 69%. This indicates that a local mechanism may not be the only cause for the overreaction of the coronary vessels. One possible transient injury is impairment of endothelial function by virus-induced inflammation, which was recently shown to occur with parvovirus B19 infection (19).

Because the clinical situation in which the chest pain leading to emergent presentation of the patient cannot be exactly reproduced, some uncertainty about the causal relationship between the observation of coronary spasm during ACH administration and the clinical event remains. We think, however, that the combination of angiographically documented spasm combined with signs of ischemia in the ECG plus exact reproduction of the symptoms leading to admission (i.e., chest pain, 42 of 50 patients with coronary spasm in the ACH test) strongly suggests a causal relationship between spasm and the clinical occurrence of ACS. Fluctuation of symptoms is well known in patients with angina caused by epicardial coronary stenosis. Hence, one might expect that the same might be true in coronary vasospasm. Therefore, asymptomatic coronary spasm in 8 of our patients may still be related to the acute chest pain, but a causal relationship is less convincing. Nevertheless, asymptomatic coronary vasospasm may be a clinically important finding because serious complications may occur in such a setting (20).

Study limitations. We did not evaluate coagulation abnormalities that were previously reported in some cases as a cause of ACS (21). However, our aim was not to provide all-encompassing information about possible causes of chest pain in patients without culprit lesion but to focus on the role of coronary spasm reproduced by ACH testing. Therefore, other possible causes of chest pain such as myocarditis were not systematically ruled out, although in a subgroup of patients this may have been the underlying cause.

Conclusions

Every fourth patient with ACS had no culprit lesion at coronary angiography. In these patients epicardial coronary spasm could be documented in 50%. Coronary spasm is a frequent cause of ACS and should regularly be considered as a differential diagnosis. Intracoronary provocation with

ACH is the gold standard for establishing the diagnosis. It reliably and safely detects coronary spasm to guide institution of appropriate therapy.

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Reprint requests and correspondence: Dr. Udo Sechtem, Robert-Bosch-Krankenhaus, Department of Cardiology and Pulmology, Auerbachstrasse 110, 70376 Stuttgart, Germany. E-mail: Udo.Sechtem@rbk.de.

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Key Words: acute coronary syndrome ■ coronary artery spasm ■ acetylcholine ■ culprit lesion ■ chest pain.